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An agency of Industry Canada

CA 2143070 C 2001/12/18

(11)(21) 2 143 070

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1995/02/21

(41) Mise à la disp. pub./Open to Public Insp.: 1995/08/23

(45) Date de délivrance/Issue Date: 2001/12/18

(30) Priorité/Priority: 1994/02/22 (08/199,933) US

(51) Cl.Int.^{6}/Int.Cl.^{6} A61K 47/30, A61K 9/10

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(54) Titre : FORMULATION PHARMACEUTIQUE SOUS FORME DE SUSPENSION LIQUIDE ADMINISTREE PAR VOIE ORALE, POUR DEGAGEMENT PROLONGE

(54) Title: ORAL CONTROLLED RELEASE LIQUID SUSPENSION PHARMACEUTICAL FORMULATION

(57) Abrégé/Abstract:
A controlled release oral formulation for use with a variety of drugs, e.g. anti-Parkinsonian, cardiovascular and anti-epileptic drugs are formed in liquid suspension form. The ingredients in the suspension are water, an edible oil and a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient, at least two water soluble biodegradable polymers, and optionally with at least one antioxidant to prevent degradation and oxidation of the pharmaceutically active ingredients. Suitable polymers are polysucrose, copolymer of sucrose and epichlorohydrin, hydroxyethyl cellulose hydroxypropyl-ethyl cellulose, hydoxypropyl-methyl cellulose, gelatine, starch, modified crosslinked starch, polyethyleneimine, methoxypolyethylene glycol, polyethylene oxide, cellulose acetate, polyvinyl alcohol, sodium alginate, N,N-diethylaminoacetate, block copolymers of polyoxyethylene, block copolymers of polyoxypropylene, a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose, and combinations thereof. Suitable edible oils are mineral oil, soyabean oil, coconut oil, vegetable oil and sunflower oil and combinations thereof. Suitable stabilizers are oleic acid, cholic acid, deoxycholic acid, pharmaceutically acceptable salts thereof and combinations thereof. Suitable antioxidants are tocopherol, deteroxime mesylate, methyl paraben and ascorbic acid. A typical teaspoon dose of anti-Parkinson liquid suspension contains 15-150 mg carbidopa, 50-1500 mg levodopa, 100-300 mg of a combination of polyvinyl alcohol and polysucrose, 10-50 mg oil, 5-15 mg antioxidant, e.g. vitamin E, 5-20 mg stabilizer, 10-15 mg colorants, 10-15 mg natural flavouring agents and 5 ml water.

Oral Controlled Release Liquid Suspension Pharmaceutical Formulation

Technical Field

The present invention relates to an improved delivery system for the administration of drugs. In particular it relates to drugs which are orally administered.

Background

One of the major problems with the administration of many drugs is the adverse reaction due to frequent dosing. Attempts have been made in the past to control the rate of release of the drug through the use of so-called controlled release tablets. However, there often is poor bioavailability of the drug due to incomplete dissolution and/or disintegration of the tablets in the gastrointestinal tract. In addition, in some instances, for example in advanced stages of Parkinson's disease, the patient finds it difficult to swallow tablets. Furthermore, it often takes several hours for the tablet to dissolve sufficiently for the patient to obtain immediate relief from the drug. It is also known that the pH in a patient's gastrointestinal tract sometimes affects the rate of release of the drug from the tablet and that the pH varies from time to time, thus making treatment or control of the disease more difficult. There is therefore a need to provide a drug delivery system which gives faster initial availability of the drug, improves the bioavailability of the drug, reduces the adverse reactions and maintains a constant plasma level of active ingredients for a prolonged time. The present invention is intended to alleviate the

aforementioned difficulties.

Disclosure of Invention

Accordingly the present invention provides a controlled release oral formulation comprising a liquid suspension of water, a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient, and at least two water soluble biodegradable polymers.

It will be recognized by those skilled in the art that for many pharmaceutical compositions it is usual to add at least one antioxidant to prevent degradation and oxidation of the pharmaceutically active ingredients.

In one embodiment the polymers are selected from the group consisting of polysucrose, copolymer of sucrose and epichlorohydrin, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-ethyl cellulose, hydroxypropyl-methyl cellulose, gelatine, starch, crosslinked starch, polyethyleneimine, polyethylene glycol, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, cellulose acetate, polyvinyl alcohol, sodium alginate, N,N-diethylaminoacetate, block copolymers of polyoxyethylene and polyoxypropylene , a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose, and combinations thereof.

In another embodiment the total concentration of polymer is present in an amount of from 20 to 60 g for every litre of water in the formulation. From a dosage standpoint, this corresponds to 100 to 300 mg total polymer for every 5 ml (teaspoon) water.

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In yet another embodiment the polymer is selected from a combination of methoxypolyethylene glycol and polyvinyl alcohol, a combination of polyethylene glycol and polyvinyl alcohol, a combination of methoxypolyethylene glycol and polysucrose, a combination of methoxypolyethylene glycol and polysucrose, a combination of starch and polysucrose, methoxypolyethylene glycol and polysucrose, polyethylene glycol and polysucrose, a combination of polyvinyl alcohol and at least one of the celluloses, and a combination of polyvinyl alcohol and polysucrose.

In a further embodiment, the formulation may include an edible oil selected from the group consisting of mineral oil, soyabean oil, coconut oil, vegetable oil and sunflower oil and combinations thereof. The edible oil may be present in an amount of from 2 to 10 g for every litre of water in the formulation.

In yet another embodiment the stabilizer is selected from the group consisting of oleic acid, cholic acid, deoxycholic acid, pharmaceutically acceptable salts thereof and combinations thereof.

In another embodiment the antioxidant is selected from the group consisting of tocopherol, deteroxime mesylate, methyl paraben and ascorbic acid.

In yet another embodiment the antioxidant is present in an amount of 1 to 3 g for every litre of water in the formulation.

In a further embodiment the stabilizer is present in an amount of from 1 to 4 g for every litre of water

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in the formulation.

It will be understood by those skilled in the art that colorants, flavouring agents and non-therapeutic amounts of other compounds may be included in the formulation.

The liquid suspension preferably has a viscosity something akin to mineral oil or castor oil.

Although this disclosure exemplifies application of the invention to anti-Parkinson's disease drugs in particular, it is also applicable to other drugs, some of which are indicated herein.

The invention also provides a controlled release oral formulation comprising a liquid suspension of water, an edible oil and a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient selected from the group consisting of anti-Parkinson drugs, dopamine agonists, anticholinergic agents, anti-cholesterol agents, anti-arthritis agents, anti-epileptic drugs, antidepressants, anti-ulcer drugs, cardiovascular drugs, hypoglycemic agents and insulin, and at least two water soluble biodegradable polymers, wherein for every litre of water there is from 20 to 60 g of the polymers, and from 2 to 10 g of the edible oil.

A preferred antioxidant to prevent degradation and oxidation of certain pharmaceutically active ingredients is tocopherol, e.g. vitamin E.

In one embodiment the active ingredient of the anti-Parkinson drug is selected from carbidopa and levodopa, benserazide and levodopa, bromocriptine,

pergolide, ergot, seligine, and lisuride.

In a further embodiment the active ingredient is carbidopa and levodopa in amounts of from 3 to 30 g carbidopa and from 10 to 300 g levodopa per litre of water.

In yet another embodiment the formulation contains from 1 to 5 g antioxidant, preferably from 2 to 3 g antioxidant per litre water. A preferred antioxidant is tocopherol, e.g. vitamin E.

A preferred formulation comprises from 3 to 30 g carbidopa, from 10 to 300 g levodopa, from 1 to 3 g of an antioxidant selected from tocopherol, deteroxime mesylate, methyl paraben and ascorbic acid, water, from 2 to 10 g of an edible oil selected from mineral oil, vegetable oil, soyabean oil, coconut oil, and sunflower oil, from 20 to 60 g total polymer, from 1 to 4 g of a stabilizer selected from oleic acid, cholic acid, deoxycholic acid, pharmaceutically acceptable salts thereof and combinations thereof, from 2 to 3 g colorant and from 2 to 3 g of a flavouring agent, said amounts being expressed for every litre of water.

Examples of anti-cholesterol agents are lovastatin, simvastatin, pravastatin, gemfibrosil and questran. Examples of anti-arthritis agents are diclofenac potassium, naproxen, catoprophen and indomethicine. Examples of antidepressants are fluoxetin, sertraline HCl, paroxetin and zopiclone. Examples of anti-ulcer H_2 receptor antagonists are ranitidine and famotidine, and other anti-ulcer drugs are omparazide, cesupride and misoprostol. Examples of ACE inhibitor cardiovascular

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drugs are analapril, lisinopril, captopril and quinapril. Examples of cardiovascular calcium channel blockers are diltiazem, verapamil, isosorbide mononitrate, nifidipine and isradipe. Another cardiovascular drug is coumarin. An example of a hypoglycaemic agent is glizipide. Insulin is used for the control of diabetes. As will be understood by those skilled in the art, two or more pharmaceutically active ingredients may be combined for specific effects. The necessary amounts of active ingredient can be determined by simple experimentation.

The invention also provides a controlled release oral anti-epileptic drug formulation comprising a liquid suspension of water, an edible oil and a stabilizer for the liquid suspension, at least one pharmaceutically active anti-epileptic ingredient, and at least two water soluble biodegradable polymers, wherein for every litre of water there is from 20 to 60 g of the polymers, and from 2 to 10 g of the edible oil.

The present invention also provides a method for making a controlled release oral formulation comprising a liquid suspension of water, an edible oil and a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient, and at least two water soluble biodegradable polymers, wherein the pharmaceutically active ingredient, the edible oil, the stabilizer and the polymers are dissolved or dispersed in water and vigorously mixed until a liquid suspension is formed.

As indicated herein above, those skilled in the art

recognize that for many pharmaceutical compositions it is usual to add at least one antioxidant to prevent degradation and oxidation of the pharmaceutically active ingredients.

In one embodiment the polymer is selected from the group consisting of polysucrose, a copolymer of sucrose and epichlorohydrin, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-ethyl cellulose, hydroxypropyl-methyl cellulose, gelatine, starch, crosslinked starch polyethyleneimine, polyethylene glycol, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, cellulose acetate, polyvinyl alcohol, sodium alginate, N,N-diethylaminoacetate, block copolymers of polyoxyethylene and polyoxypropylene , a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose, and combinations thereof.

In another embodiment the polymer is added in an amount of from 20 to 60 g of total polymer for every litre of water in the formulation.

In yet another embodiment the polymer is selected from a combination of methoxypolyethylene glycol and polyvinyl alcohol, a combination of methoxypolyethylene glycol and polysucrose, a combination of polyvinyl alcohol and at least one of the celluloses, a combination of polysucrose and gelatine, and a combination of polyvinyl alcohol and polysucrose.

The most preferred combinations are polysucrose and cellulose, polysucrose and polyethylene glycol, and polysucrose and gelatine.

In a further embodiment the edible oil is selected from the group consisting of mineral oil, soyabean oil, coconut oil, vegetable oil and sunflower oil and combinations thereof.

The most preferred edible oil is coconut oil. In yet another embodiment the edible oil is added in an amount of from 2 to 10 g for every litre of water in the formulation.

In yet another embodiment the stabilizer is selected from the group consisting of oleic acid, cholic acid, deoxycholic acid, pharmaceutically acceptable salts thereof and combinations thereof.

In another embodiment the antioxidant is selected from the group consisting of tocopherol, deteroxime mesylate, methyl paraben and ascorbic acid.

In yet another embodiment the antioxidant is added in an amount of 1 to 3 g for every litre water.

In a further embodiment the stabilizer is added in an amount of from 1 to 4 g for every litre of water in the formulation.

In another embodiment, vigorous mixing is accomplished using a turbine mixer or ribbon blender.

The invention provides a method for making a controlled release oral drug formulation comprising a liquid suspension of water, an edible oil and a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient selected from the group consisting of anti-Parkinson drugs, dopamine agonists, anticholinergic agents, anti-cholesterol agents, anti-arthritis agents, anti-epileptic drugs,

antidepressants, anti-ulcer drugs, cardiovascular drugs, hypoglycemic agents and insulin, and at least two water soluble biodegradable polymers, wherein there is added from 20 to 60 g of the polymers, and from 2 to 10 g of the edible oil for every litre of water, and wherein the pharmaceutically active ingredient, the edible oil, the stabilizer and the polymers are dissolved or dispersed in water and vigorously mixed until a liquid suspension is formed.

As indicated hereinabove, an antioxidant for the pharmaceutically active ingredient is usually added.

In one embodiment the active ingredient of the anti-Parkinson drug is selected from carbidopa and levodopa, bromocriptine, pergolide, ergot, seligiline, and lisuride.

In a further embodiment the active ingredient is carbidopa and levodopa in amounts of from 3 to 30 g carbidopa and from 10 to 300 g levodopa per litre of water.

In yet another embodiment from 1 to 3 g antioxidant is added to the formulation, e.g. from 2 to 3 g vitamin E per litre of water.

A preferred method for making an anti-Parkinson controlled release formulation comprises adding from 3 to 30 g carbidopa, from 10 to 300 g levodopa, from 1 to 3 g of an antioxidant selected from tocopherol, deteroxime mesylate, methyl paraben and ascorbic acid, from 2 to 10 g of an edible oil selected from mineral oil, vegetable oil, soyabean oil, coconut oil, and sunflower oil, from 20 to 60 g total polymer, from 1 to

4 g of a stabilizer selected from oleic acid, cholic acid, deoxycholic acid, pharmaceutically acceptable salts thereof and combinations thereof, from 2 to 3 g colorant and from 2 to 3 g of a flavouring agent, to water, said amounts being expressed for every litre water, and vigorously mixing until a liquid suspension is formed.

Examples of anti-cholesterol agents are lovastatin, simvastatin, pravastatin, gemfibrosil and questran. Examples of anti-arthritis agents are diclofenac potassium, naproxen, catoprophen and indomethicine. Examples of antidepressants are fluoxetin, sertraline HCl, paroxetin and zopiclone. Examples of anti-ulcer H_2 receptor antagonists are ranitidine and famotidine, and other anti-ulcer drugs are omparazide, cesupride and misoprostol. Examples of ACE inhibitor cardiovascular drugs are enalapril, lisinopril, captopril and quinapril. Examples of cardiovascular calcium channel blockers are diltiazem, verapamil, isosorbide mononitrate, nifidipine and isradipe. Another cardiovascular drug is coumarin. An example of a hypoglycaemic agent is glizipide. Insulin is used for the control of diabetes.

The method of making the controlled release formulation is easy to do. The concentrations of the components of the formulation are adjusted until the resulting suspension has a liquid consistency, so that it is easily ingested and swallowed. A preferred consistency is like mineral oil or castor oil. The relative amounts of the components is found by easy

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experimentation. Mixing of the components may be accomplished by vigorous stirring, vigorous shaking of the vessel which contains the components, sonication, use of high speed mixers or by other methods known to those skilled in the art of making liquid suspensions.

In the selection of a suitable polymer combination, it has been found that the amount of total polymer should be less than about 60 g for every litre of water. Preferably the amount of polyvinyl alcohol is less than about 30 g. Polyvinyl alcohol has the advantage of preventing the release of the drug over a long period of time. This of course is a disadvantage for immediate release of a drug. Accordingly it is desirable to combine polyvinyl alcohol with one of the other, more easily dissolved polymers such as polysucrose or one of the celluloses. Preferred combinations are methoxypolyethylene glycol and polyvinyl alcohol, polysucrose and polyvinyl alcohol, polyvinyl alcohol and cellulose, and methoxypolyethylene glycol and polysucrose.

Advantages of the present formulation are that adverse reactions are decreased, bioavailability is increased, gastrointestinal side effects are decreased, wearing-off is lessened, on-off dyskinesia and other central nervous system (CNS) effects are greatly improved, when compared to commercial controlled release tablets. A further advantage of the formulation and method over current commercial practices, e.g. tabletting and regular capsules, is that the capital and manufacturing costs are lower.

In the treatment of Parkinson's disease for

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example, with carbidopa and levodopa, the present formulation will provide relief within about 30 minutes, compared to about 3 to 4 hours for commercially available controlled release tablets. Additionally the present formulation will maintain a relatively constant level of active drug in the patient for a prolonged period of time, for example 6 or more hours, thus providing a longer lasting action and response to treatment. Furthermore, fewer applications are needed and high blood levels, which may cause dyskinesia, tend to be avoided. Recommended daily doses will be 3 to 4 teaspoons (15 to 20 ml). That is, one teaspoon may be taken every 6 to 7 hours.

For the treatment of Parkinson's disease a typical formulation would comprise 200 mg levodopa, 50 mg carbidopa, 200 mg of one or a combination of the water soluble polymers, 20 mg coconut oil, 15 mg antioxidant for the levodopa/carbidopa, 15 mg stabilizer, 10 mg colorants and 15 mg flavouring agents and 5 ml water. To prepare the formulation these ingredients (in scaled-up quantities) may be dissolved or dispersed in a sterile brown glass container and vigorously stirred until a uniform suspension is formed. The suspension so formed would have a liquid consistency, suitable for oral administration by spoon. Preferably the consistency is about that of castor oil.

The invention is further illustrated by the following non-limiting examples.

Example I

Two samples were prepared, each having 40 mg of L-

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dopa, 12 mg of carbidopa, 300 mg of polyethylene glycol (PEG) and 300 mg of polysucrose (PS), mixed with 0.75 ml distilled water, to form a suspension. The mixture was gavaged orally to rats. Blood samples were taken from the rats at either 30 minute or 60 minute intervals. The blood samples were centrifuged to isolate the plasma. The plasma was then analyzed for the L-dopa concentration using HPLC techniques.

It will be noted that the polymer concentration is about 800 g/l. This is because the formulation is intended to be given to rats, whose metabolism is far faster than in human beings. Lower concentrations would required for administration to humans.

A control sample was prepared from 40 mg L-dopa and 12 mg carbidopa mixed with 0.75 ml distilled water, i.e. no polymer mixture was present. The sample was also gavaged orally to a rat and blood samples taken and analyzed similarly.

The results of the analyses are shown in Table I.

Table I

Time	Control (μg/ml)	PEG/PS Suspension (mins.) (μg/ml)
30	2.0	3.0
60	3.5	4.1
120	6.4	4.4
180	4.2	5.8
240	2.8	5.6
300	2.5	5.2
360	2.2	4.8
420	1.9	4.8

This table illustrates more controlled release of the L-dopa when administered with the polymer suspension.

Example II

The experiment of Example I was repeated except the suspension was made additionally with 15 mg ascorbic acid as an antioxidant for the L-dopa and carbidopa. After 7 weeks and the sample was gavaged to a rat. Again, blood samples were taken and analyzed as in Example I.

A control sample was prepared from a commercially available tablet, crushed into powder. The sample contained about 40 mg L-dopa and 12 mg carbidopa. No polymer mixture was present. The sample was also gavaged orally to a rat and blood samples taken and analyzed similarly.

The results are shown in Table II.

Table II

Time (mins.)	PEG/PS Suspension (μg/ml)	Tablet Powder (μg/ml)
30	2.8	1.9
60	4.1	3.7
120	4.3	4.7
180	6.9	5.5
240	6.2	5.2
300	5.4	4.8
360	5.3	3.7
420	4.9	3.2

This table again illustrates extended, controlled release of the L-dopa when administered with the polymer suspension.

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CLAIMS:

1. A controlled release oral formulation comprising a liquid suspension of water, a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient, and at least two water soluble biodegradable polymers, wherein the polymers are selected from the group consisting of polysucrose, copolymer of sucrose and epichlorohydrin, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-ethyl cellulose, hydroxypropyl-methyl cellulose, gelatine, starch, crosslinked starch, polyethyleneimine, polyethylene glycol, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, cellulose acetate, polyvinyl alcohol, sodium alginate, N,N-diethylaminoacetate, block copolymers of polyoxyethylene and polyoxypropylene , a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose, and combinations thereof, with the proviso that when one of the biodegradable polymers is selected from the group consisting of hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-ethyl cellulose, hydroxypropyl-methyl cellulose, gelatine, cellulose acetate, polyvinyl alcohol, block copolymers of polyoxyethylene and polyoxypropylene and a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose, then other biodegrable polymers are selected from the group consisting of polysucrose, copolymer of sucrose and epichlorohydrin, starch, crosslinked starch,

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polyethyleneimine, polyethylene glycol, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, sodium alginate, N,N-diethylaminoacetate and combinations thereof.

2. A formulation according to Claim 1 wherein the total concentration of polymer is present in an amount of from 20 to 60 g for every litre of water in the formulation.

3. A formulation according to Claim 1 wherein the polymers are selected from a combination of methoxypolyethylene glycol and polyvinyl alcohol, a combination of polyethylene glycol and polyvinyl alcohol, a combination of methoxypolyethylene glycol and polysucrose, a combination of starch and polysucrose, a combination of methoxypolyethylene glycol and polysucrose, a combination of polyethylene glycol and polysucrose, and a combination of polyvinyl alcohol and polysucrose.

4. A formulation according to Claim 1 further comprising an edible oil selected from the group consisting of mineral oil, soyabean oil, coconut oil, vegetable oil and sunflower oil and combinations thereof.

5. A formulation according to Claim 4 wherein the edible oil is present in an amount of from 2 to 10 g for every litre of water in the formulation.

6. A formulation according to Claim 1 wherein the pharmaceutically active ingredient is selected from the group consisting of anti-Parkinson drugs, dopamine agonists, anticholinergic agents, anti-cholesterol agents, anti-arthritis agents, anti-epileptic drugs, antidepressants, anti-ulcer drugs, cardiovascular drugs,

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and hypoglycemic agents.

7. A formulation according to Claim 1 wherein the pharmacutically active ingredient is selected from the group consisting of lovastatin, simvastatin, pravastatin, gemfibrosil, questran, diclofenac potassium, naproxen, catoprophen, indomethicine, fluoxetin, sertraline HCl, paroxetin, zopiclone, ranitidine, famotidine, omparazide, cesupride, misoprostol, enalapril, lisinopril, captopril, quinapril, diltiazem, verapamil, isosorbide mononitrate, nifidipine, isradipe, coumarin, and glizipide.

8. A formulation according to Claim 1 wherein the pharmaceutically active drug is an anti-Parkinson drug selected from the group consisting of carbidopa and levodopa, benserazide and levodopa, bromocriptine, pergolide, ergot, seligiline, and lisuride.

9. A formulation according to Claim 8 comprising from 3 to 30 g carbidopa, from 10 to 300 g levodopa, from 1 to 3 g of an antioxidant selected from tocopherol, deteroxime mesylate, methyl paraben and ascorbic acid, water, from 2 to 10 g of an edible oil selected from mineral oil, vegetable oil, soyabean oil, coconut oil, and sunflower oil, from 20 to 60 g total polymer, from 1 to 4 g of a stabilizer selected from oleic acid, cholic acid, deoxycholic acid, pharmaceutically acceptable salts thereof and combinations thereof, from 2 to 3 g colorant and from 2 to 3 g of a flavouring agent, said amounts being expressed for every litre of water.

10. A method for making a controlled release oral formulation comprising a liquid suspension of water,

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a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient, and at least two water soluble biodegradable polymers, wherein the pharmaceutically active ingredient, the stabilizer and the polymers are dissolved or dispersed in water and vigorously mixed until a liquid suspension is formed, and wherein the polymers are selected from the group consisting of polysucrose, copolymer of sucrose and epichlorohydrin, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-ethyl cellulose, hydroxypropyl-methyl cellulose, gelatine, starch, crosslinked starch, polyethyleneimine, polyethylene glycol, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, cellulose acetate, polyvinyl alcohol, sodium alginate, N,N-diethylaminoacetate, block copolymers of polyoxyethylene and polyoxypropylene , a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose, and combinations thereof, with the proviso that when one of the biodegradable polymers is selected from the group consisting of hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-ethyl cellulose, hydroxypropyl-methyl cellulose, gelatine, cellulose acetate, polyvinyl alcohol, block copolymers of polyoxyethylene and polyoxypropylene and a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose, then other biodegrable polymers are selected from the group consisting of polysucrose, copolymer of sucrose and epichlorohydrin, starch, crosslinked

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starch,polyethyleneimine, polyetehylene glycol, methoxypolyethylene glycol, ethoxypolyethylene glycol, polyethylene oxide, sodium alginate, N,N-diethylaminoacetate and combinations thereof.

11. A method according to Claim 10 wherein the total concentration of polymer is present in an amount of from 20 to 60 g for every litre of water in the formulation.

12. A method according to Claim 10 wherein the polymers are selected from a combination of methoxypolyethylene glycol and polyvinyl alcohol, a combination of polyethylene glycol and polyvinyl alcohol, a combination of methoxypolyethylene glycol and polysucrose, a combination of starch and polysucrose, a combination of methoxypolyethylene glycol and polysucrose, a combination of polyethylene glycol and polysucrose, and a combination of polyvinyl alcohol and polysucrose.

13. A method according to Claim 10 wherein the formulation further comprises an edible oil selected from the group consisting of mineral oil, soyabean oil, coconut oil, vegetable oil and sunflower oil and combinations thereof, the edible oil being vigorously mixed with the water, stabilizer and the polymers to form the liquid suspension.

14. A method according to Claim 13 wherein the edible oil is present in an amount of from 2 to 10 g for every litre of water in the formulation.

15. A method according to Claim 10 wherein a controlled release oral liquid suspension formulation is made by dissolving or dispersing in water, an edible oil and a stabilizer for pharmaceutically active ingredient selected from the group consisting of anti-Parkinson drugs, dopamine agonists, anticholinergic agents, anti-cholesterol agents, anti-arthritis agents, anti-

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epileptic drugs, antidepressants, anti-ulcer drugs, cardiovascular drugs, and hypoglycemic agents, and at least two water soluble biodegradable polymers, wherein for every litre of water there is from 20 to 60 g of the polymers, and from 2 to 10 g of the edible oil, and vigorously mixing until a liquid suspension is formed.

16. A method according to Claim 10 wherein a controlled release oral liquid suspension formulation is made by dissolving or dispersing in water, an edible oil and a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient selected from the group consisting of lovastatin, simvastatin, pravastatin, gemfibrosil, questran, diclofenac potassium, naproxen, catoprophen, indomethicine, fluoxetin, sertraline HCl, paroxetin, zopiclone, ranitidine, famotidine, omparazide, cesupride, misoprostol, enalapril, lisinopril, captopril, quinapril, diltiazem, verapamil, isosorbide mononitrate, nefidipine, isradipe, coumarin, and glizipide.

17. A method according to Claim 10 wherein the pharmaceutically active ingredient is an anti-Parkinsonian drug selected from the group consisting of carbidopa and levodopa, benserazide and levodopa, bromocriptine, pergolide, ergot, seligiline, and lisuride.

18. A method according to Claim 17 wherein from 3 to 30 g carbidopa, from 10 to 300 g levodopa, from 1 to 3 g of an antioxidant selected from tocopherol, deteroxime mesylate, methyl paraben and ascorbic acid, water, from

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2 to 10 g of an edible oil selected from mineral oil, vegetable oil, soyabean oil, coconut oil, and sunflower oil, from 20 to 60 g total polymer, from 1 to 4 g of a stabilizer selected from oleic acid, cholic acid, deoxycholic acid, pharmaceutically acceptable salts thereof and combinations thereof, from 2 to 3 g colorant and from 2 to 3 g of a flavouring agent, said amounts being expressed for every litre of water, are dissolved or dispersed in water and then vigorously mixed until a liquid suspension is formed.

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ABSTRACT OF THE DISCLOSURE

A controlled release oral formulation for use with a variety of drugs, e.g. anti-Parkinsonian, cardiovascular and anti-epileptic drugs are formed in liquid suspension form. The ingredients in the suspension are water, an edible oil and a stabilizer for the liquid suspension, at least one pharmaceutically active ingredient, at least two water soluble biodegradable polymers, and optionally with at least one antioxidant to prevent degradation and oxidation of the pharmaceutically active ingredients. Suitable polymers are polysucrose, copolymer of sucrose and epichlorohydrin, hydroxyethyl cellulose hydroxypropyl-ethyl cellulose, hydoxypropyl-methyl cellulose, gelatine, starch, modified crosslinked starch, polyethyleneimine, methoxypolyethylene glycol, polyethylene oxide, cellulose acetate, polyvinyl alcohol, sodium alginate, N,N-diethylaminoacetate, block copolymers of polyoxyethylene, block copolymers of polyoxypropylene, a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose, and combinations thereof. Suitable edible oils are mineral oil, soyabean oil, coconut oil, vegetable oil and sunflower oil and combinations thereof. Suitable stabilizers are oleic acid, cholic acid, deoxycholic acid, pharmaceutically acceptable salts thereof and combinations thereof. Suitable antioxidants are tocopherol, deteroxime mesylate, methyl paraben and ascorbic acid.

A typical teaspoon dose of anti-Parkinson liquid suspension contains 15-150 mg carbidopa, 50-1500 mg

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levodopa, 100-300 mg of a combination of polyvinyl alcohol and polysucrose, 10-50 mg oil, 5-15 mg antioxidant, e.g. vitamin E, 5-20 mg stabilizer, 10-15 mg colorants, 10-15 mg natural flavouring agents and 5 ml water.

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